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Attachment anxiety is related to Epstein–Barr virus latency

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ABSTRACT

Attachment theory provides a framework for understanding individual differences in chronic interpersonal stress. Attachment anxiety, a type of relationship insecurity characterized by worry about rejection and abandonment, is a chronic interpersonal stressor. Stress impacts cellular immunity, including herpesvirus reactivation. We investigated whether attachment anxiety was related to the expression of a latent herpesvirus, Epstein–Barr virus (EBV), when individuals were being tested for breast or colon cancer and approximately 1 year later. Participants ($N = 183$) completed a standard attachment questionnaire and provided blood to assess EBV viral capsid antigen (VCA) IgG antibody titers. Individuals with more attachment anxiety had higher EBV VCA IgG antibody titers than those with less attachment anxiety. The strength of the association between attachment anxiety and antibody titers was the same at both assessments. This study is the first to show an association between latent herpesvirus reactivation and attachment anxiety. Because elevated herpesvirus antibody titers reflect poorer cellular immune system control over the latent virus, these data suggest that high attachment anxiety is associated with cellular immune dysregulation.

1. Introduction

There are well-documented links between close relationships and physical health. People who have supportive close relationships have lower rates of morbidity and mortality than those who have unsupportive and conflict-ridden relationships (Berkman and Syme, 1979; Brummett et al., 2001; Gilbert et al., 2009; House, 1988; Orth-Gomer and Johnson, 1987; Repetti et al., 2002; Tomaka et al., 2006; Uchino et al., 1996). Attachment theory provides a framework for understanding individual differences in chronic interpersonal stress and thus may offer insight into the associations between close relationships and health (Diamond and Hicks, 2004; Shaver and Mikulincer, 2007; Uchino, 2009).

Attachment theory suggests that people who have responsive and supportive parents during childhood develop a sense of emotional security that lasts into adulthood, while those who have unresponsive and unsupportive parents develop a sense of emotional insecurity (Mikulincer and Shaver, 2009; Thompson, 1999). Different academic and theoretical traditions conceptualize attachment insecurity in slightly different ways (Fraley and Waller, 1998); according to adult attachment theory, there are two patterns or dimensions of attachment insecurity: attachment anxiety and attachment avoidance (Mikulincer and Shaver, 2007). These patterns have the potential to change throughout one's lifespan but are thought to be relatively stable (Mikulincer and Shaver, 2007).

People with high attachment anxiety constantly worry about rejection and abandonment and use "hyperactivating" coping strategies, such as excessive rumination and preoccupation about

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stressful events (Brennan et al., 1998; Diamond and Fagundes, 2010; Diamond, 2001; Fraley and Shaver, 2000a). Indeed, people with higher attachment anxiety tend to have a more negative self-image and intense negative emotions than those with lower attachment anxiety (Mikulincer et al., 2006; Pietromonaco and Barrett, 1997).

People with high attachment avoidance are uncomfortable depending on others for support and use "deactivating" coping strategies that inhibit, exclude, or suppress distressing relational experiences (Brennan et al., 1998; Fraley and Shaver, 2000b). Individuals with higher attachment avoidance tend to denigrate and distrust support providers more than those with lower attachment avoidance (Mikulincer and Shaver, 2003; Shaver and Mikulincer, 2005). Furthermore, they keep negative emotions alive internally, while attempting not to express them externally (Mikulincer and Shaver, 2003; Shaver and Mikulincer, 2005).

Attachment anxiety has been reliably linked to many age-related health problems, while attachment avoidance has not (McWilliams and Bailey, 2010; Puig et al., 2012). The chronic social stress that is a feature of attachment anxiety may be an important mechanism underlying this link; chronic stress can impair vaccine responses, slow wound healing, promote inflammation, and dysregulate cellular immunity (Glaser and Kiecolt-Glaser, 2005a). Consistent with this argument, recent work in the field of psychoneuroimmunology demonstrated that people who had higher attachment anxiety had fewer numbers of $CD3^+$ T-cells, $CD45^+$ T-cells, $CD3^+CD4^+$ helper T-cells, and $CD3^+CD8^+$ cytotoxic T-cells compared with those who had lower attachment anxiety (Jaremka et al., 2013).

Chronic interpersonal stress can drive herpesvirus reactivation and replication by impairing cellular immune system control over viral latency through both autonomic and glucocorticoid pathways (Cacioppo et al., 2002; Glaser and Kiecolt-Glaser, 1994; Yang et al., 2010). Maladaptive alterations in cellular immune function can enhance herpesvirus reactivation and replication, resulting in elevated herpesvirus antibody titers (Glaser and Kiecolt-Glaser, 1994, 2005b; Glaser et al., 2005; Steptoe et al., 2007). For example, organ transplant patients have dysregulated cellular immunity and elevated herpesvirus antibody titers (Gray et al., 1995). Although usually asymptomatic, elevated herpesvirus antibody titers reflect poorer cellular immune system control over viral latency (Glaser and Kiecolt-Glaser, 1994). Accordingly, people who are anxiously attached may be vulnerable to latent herpesvirus reactivation and replication due to their chronic interpersonal stress and corresponding cellular immune dysregulation.

Based on the argument that attachment anxiety is a chronic interpersonal stressor, we hypothesized that those who were more anxiously attached would have higher EBV VCA IgG antibody titers than those who were less anxiously attached. Because most studies have not shown a consistent association between attachment avoidance and health or stress sensitivity, we made no a priori hypothesis about attachment avoidance (Dewitte et al., 2010; Jaremka et al., 2013). However, we examined the possibility that those who were more avoidantly attached would have higher EBV VCA IgG antibody titers than those who were less avoidantly attached. We also explored whether the association between attachment anxiety/avoidance and herpesvirus reactivation differed over time.

2. Methods

2.1. Participants and procedure overview

Study participants ($N = 183$) were recruited from oncology clinics as they were being tested for breast or colon cancer as part of an ongoing longitudinal observational study investigating potential links between fatigue and immune dysregulation. Participants were being tested for breast or colon cancer because of a suspicious initial test; all participants completed their first visit after this initial suspicious test. Participants eventually received a benign diagnosis as the result of one or more follow-up tests. On average, participants received a benign diagnosis from their final test 9.8 days ($SD = 15.08$) after their first study visit. Approximately one year later, participants completed a follow-up assessment. We did not have data for 12% of participants at the second assessment. Participants who did not complete the second visit were contacted by phone and email multiple times and (a) stated they did not want to continue due to lack of time or interest, or (b) never returned our messages. Screening exclusions included a prior history of cancer except basal or squamous cell skin cancers and severe cognitive impairment (e.g., Alzheimer's disease). Out of the 183 participants enrolled at the first visit, eight were EBV seronegative (i.e., they never contracted EBV); therefore, they were not included in the analyses. All participants who were EBV seropositive at the first visit were also seropositive at the second visit; once contracted, herpesvirus seropositivity does not change. The average time between study visits was 365 days ($SD = 124$ days). The Institutional Review Board approved the project; all subjects gave written informed consent prior to participation.

2.2. Determination of EBV VCA IgG antibody titers in plasma

EBV VCA IgG represents the antibody response to the combination of multiple viral proteins that make up the virus coat. We assessed antibody against EBV VCA IgG in plasma to assess control over viral latency. Plasma was stored at $-80\ ^\circ C$ until assayed with Euroimmun EBV ELISA plates (Boonton Township, NJ). This ELISA's antigen, a cell lysate of human B-cells infected with EBV strain P3HR-1, comprises various viral capsid proteins, including p22, gp33, gp40, gp41, gp42, gp116. EBV-VCA IgG antibody titers were assessed following instructions, with kit controls (one positive sample, one negative sample, and three calibrators) run in duplicate. After the initial 1:101 dilution, six serial two-fold dilutions of each sample were assayed, and the last positive value was the IgG antibody titer. Calculated viral titers for each sample were plotted and samples were rerun if the end point did not fall within the linear range (±15%).

2.3. Self-report measures

2.3.1. Attachment insecurity

Attachment insecurity was assessed using a modified version of the Experiences in Close Relationships (ECR-M16) scale (Lo et al., 2009). The ECR-M16 was designed to assess attachment insecurity in patients of diverse ages. The 16-item self-report measure assesses general attachment insecurity in close relationships; it contains two 8-item subscales, one assessing attachment anxiety and the other assessing attachment avoidance. The anxiety subscale includes items such as "I worry about being abandoned" and "I need a lot of reassurance that I am loved by people with whom I feel close to." The following items are representative of the avoidance scale: "I get uncomfortable when other people want to be very close to me," and "I don't feel comfortable opening up to other people." Both scales have high internal and test-retest reliability (Lo et al., 2009).

2.3.2. Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) assesses general anxiety symptoms. The BAI can discriminate between clinically anxious and non-clinically anxious people and has good test-retest reliability and internal consistency. The BAI provided a way to disentangle general anxiety from attachment anxiety (Steer and Beck, 1997).